Discovery and Characterization of BHV-7000: A Novel Kv7.2/7.3 Activator for the Treatment of Epilepsy

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Kv7 Potassium Channels Exquisitely Regulate Neuronal Firing

Kv7.2/7.3 channels are low-threshold voltage-gated potassium channels expressed in the CNS that modulate neuronal excitability¹

- Mutations in Kv7.2/7.3 channels lead to seizures or other epileptic syndromes
- Preclinical studies have shown that activating Kv7.2/7.3 hyperpolarizes RMP, increases AP threshold, and has potent anti-seizure effects
- Kv7.2/7.3 channels are a clinically validated drug target

Precision targeting of Kv7 potassium channels may deliver robust efficacy while minimizing the risk of adverse effects associated with traditional anti-epileptic drugs

Overview of Methods

- A screening tier was designed to discover potent and selective Kv7.2/7.3 activators
- Fluorescent and electrophysiological assays were employed to characterize lead compounds
- Antiseizure efficacy was evaluated in rats in the maximal electroshock seizure (MES) model and tolerability was assessed by neurological score (NS)
- Standard ADME and toxicology assays, including assessment of brain drug levels, were used to progress a candidate to the clinic
- A first-in-human phase 1 single ascending dose / multiple ascending dose (SAD/MAD) study assessed safety, tolerability, and pharmacokinetics in healthy subjects
Effects of BHV-7000 on $V_{1/2}$, RMP, and AP threshold

Voltage-dependence of activation

<table>
<thead>
<tr>
<th></th>
<th>0.3 µM</th>
<th>1.0 µM</th>
<th>3.0 µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{1/2}$ shift</td>
<td>-7.60</td>
<td>-15.21</td>
<td>-20.97</td>
</tr>
</tbody>
</table>

**P<0.01
BHV-7000: Delivering potent anti-seizure effects with a wide tolerability index in the rat MES model

Purposefully dialed-out GABA<sub>A</sub> positive allosteric modulation

Targeted Kv7 activation enables seizure protection without impacting neurobehavior

*P<0.05
BHV-7000 Phase I SAD/MAD Study: Well-tolerated without typical CNS adverse events seen with anti-seizure medications

Safety
- Single doses up to 100 mg and multiple doses up to 40 mg daily x15 days generally well-tolerated
- Most AEs mild and resolved spontaneously
- No serious or severe AEs
- No dose-limiting toxicities

Pharmacokinetics
- Target plasma concentrations for efficacy exceeded based on preclinical MES model
- High-fat meal had no effect on exposures

<table>
<thead>
<tr>
<th>Adverse Event*</th>
<th>BHV-7000 MAD pooled (n=17)</th>
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<tbody>
<tr>
<td>Somnolence</td>
<td>0%</td>
</tr>
<tr>
<td>Headache</td>
<td>18%</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0%</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>0%</td>
</tr>
<tr>
<td>Sensory disturbance</td>
<td>0%</td>
</tr>
<tr>
<td>Speech disorder</td>
<td>0%</td>
</tr>
</tbody>
</table>

*MedDRA® Preferred Term within the System Organ Class of “Nervous System Disorders”. AE, adverse event; MAD, multiple ascending dose; MES, maximal electroshock seizure; SAD, single ascending dose
Conclusions

• BHV-7000 is a novel and differentiated activator of Kv7.2/7.3 channels
• BHV-7000 is structurally and pharmacologically distinct from ezogabine
• BVH-7000 “dials-out” GABA_A receptor activation
• BHV-7000 is potent in the MES epilepsy model without impact on neurobehavior
• BHV-7000 was well-tolerated in Phase 1 SAD/MAD studies without CNS adverse effects typical of anti-seizure medications
Thank You!